schematically in Figure 3 of the specification, is a prior art three-plasmid expression system. No new matter has been added with this specification amendment.

Claim Amendments

Claims 1, 5, 7, 8, 12, 16, 20, 22, 23, 27, 31 and 35 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Support for the amendment to the claims can be found in the specification, for example, at page 9, lines 17-24; page 10, lines 13-20; page 11, lines 4-16; page 11, line 21 to page 12, line 9; page 12, line 22 to page 13, line 2; page 15, lines 3-22; page 16, lines 5-12; page 16, line 21 to page 17, line 1; page 2, line 7 to page 4, line 9; page 4, lines 19-27; page 5, lines 4-12; page 5, lines 17-25; and page 6, lines 3-11.

Paragraph 1: Restriction Requirement

Responsive to the Restriction Requirement, Applicants affirm the election of the claims of Group I (Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37), drawn to methods of making packaging cell lines, packaging cell lines and particles made by packaging cell lines, for prosecution. Applicants reserve the right to file a continuing application or take such other appropriate action as deemed necessary to protect the invention of Group II (Claims 39-43), Group III (Claims 4, 6, 11, 15, 19, 21, 26, 30, 34, 38 and 44-46) and Group IV (Claims 4, 6, 11, 15, 19, 21, 26, 30, 34, 38 and 47-49). Applicants do not hereby abandon or waive any rights in the Group II, III and IV invention(s).

Paragraph 2: Rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

As amended, the claims indicated include the following changes, made in response to the specific rejections made by the Examiner:

a) Claims 1, 8, 12, 16, 23, 27, 31 and 35 have been rejected as vague and indefinite in the recitation of the phrase "..for producing a viral accessory protein independent.." because, in the Examiner's assessment, the phrase "is only an intended use for the packaging cell lines which has little patentable weight because the claim stands on its own."

As suggested by the Examiner, Claims 1, 8, 16 and 23 have been amended to indicate that production of retroviral vector particles is a property of the packaging cell lines, thereby obviating this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

Regarding Claims 12, 27, 31 and 35, these claims do not include the phrase "..for producing a viral accessory protein independent..". In addition, Claims 12, 27, 31 and 35 also do not relate to packaging cell lines or methods of producing packaging cell lines. Rather, Claims 12 and 27 relate to methods of producing HIV-derived (Claim 12) or lentivirus-derived (Claim 27) retroviral vector particles. Claims 31 and 35 relate to HIV-derived (Claim 31) or lentivirus-derived (Claim 35) retroviral vector particles having no viral accessory proteins. Accordingly, this aspect of the rejection under 35 U.S.C. § 112, second paragraph, should not apply to Claims 12, 27, 31 and 35.

b) Claims 1, 8, 12, 16, 23, 27, 31 and 35 have been further rejected as vague and indefinite in the recitation of the phrase "accessory protein independent" because, in the Examiner's assessment, the metes and bounds of the limitation are unclear. The Examiner argues that although "[u]pon reading the specification it appears applicants intend the limitation to specify that no accessory proteins are present or expressed in the claimed packaging systems and that no constitutively expressed transport element (CTEs) are to be expressed either", "the inclusion of Figure 3 in the specification in which a three plasmid system for packaging HIV-1 particles is featured, and which clearly allows expression of most of the accessory proteins (but not *vpu*), seems to indicate that the phrase refers to systems where only some of the accessory proteins are not present or expressed." Applicants respectfully disagree with the Examiner's assessment that the metes and bounds of the phrase "accessory protein independent" are unclear, when read in light of the specification.

However, in an effort to advance prosecution in the subject application, Claims 1, 8, 12, 16, 23, 27, 31 and 35 have been amended to delete the phrase "..accessory protein independent..", thereby rendering moot this aspect of the under 35 U.S.C. § 112, second paragraph.

c) Claims 1, 5, 7-8, 12, 16, 20, 22-23, 27, 31 and 35 have been rejected as vague and indefinite in the recitation of the phrase "mutagenized to improve expression" because, in the Examiner's assessment, the metes and bounds of the phrase are unclear. More specifically, the Examiner alleges that it is unclear "what type and degree of changes to *gagpol* are encompassed by the phrase" and "what is considered the baseline for expression of *gagpol*." Applicants respectfully disagree with the Examiner's assessment that the metes and bounds of the phrase "mutagenized to improve expression" are unclear, when read in light of the specification.

However, in an effort to advance prosecution in the subject application, Claims 1, 5, 7-8, 12, 16, 20, 22-23, 27, 31 and 35 have been amended to delete the phrase "mutagenized to improve expression" and to recite "codon optimized". Support for the amendment is found in the specification, for example, at page 9, lines 21-24; page 10, lines 18-20; page 11, lines 4-7; page 11, line 21 to page 12, line 9; page 2, line 7 to page 4, line 9; page 4, lines 19-23; page 5, lines 4-8; page 5, lines 17-22; page 6, lines 3-8.

Paragraph 3: Rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 Under 35 U.S.C. § 103(a)

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Naldini *et al.* (*Science.*, 272:263-267 (1996); AR on Form PTO-1449) in view of Haas *et al.* (*Current Biology*, 6(3):315-324 (1996); AV on Form PTO-1449).

Teachings of the Cited References

Naldini *et al.*

Naldini *et al.* teach a three-plasmid expression system used to generate HIV-derived retroviral vector particles by transient transfection of mammalian cells. This three-plasmid system features (a) a first plasmid (also referred to as "the packaging construct") comprising wildtype coding sequences for HIV gagpol and coding sequences for all HIV accessory proteins, except the accessory protein Vpu; (b) a second plasmid comprising a heterologous envelope protein; and (c) a third plasmid (also referred to as "the transfer vector") containing HIV cis-acting sequences required for packaging, reverse transcription and integration, as well as restriction sites for cloning of heterologous complementary DNAs (cDNAs) of interest. Naldini *et al.* teach that all accessory proteins, except the accessory protein Vpu, are expressed by the

HIV-derived retroviral vector particles generated using their three-plasmid expression system (Naldini *et al.*, e.g., page 263, column 1, last paragraph; and Figure 1).

Importantly, Naldini *et al.* report that the design of their three-plasmid expression system "allow[s] the efficient transcription and cytoplasmic export of full-length vector transcripts only in the presence of HIV Tat and Rev regulatory proteins, both of which are encoded by the packaging plasmid" and that "[i]n the absence of these transacting factors, the only detectable expression originated from the internal promoter in the vector" (Naldini *et al.*, page 263, column 3, lines 12-24). Accordingly, Naldini *et al.* teach way from retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev proteins and Rev response element (RRE)), and particularly retroviral vector particles lacking viral accessory proteins Tat and Rev. Naldini *et al.* teach away from packaging cell lines which comprise a packaging construct comprising a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements. Naldini *et al.* also teach away from methods of producing packaging cell lines which comprise co-transfecting mammalian host cells with a packaging construct comprising a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements. In addition, Naldini *et al.* do not teach or suggest mutagenizing a *gagpol* coding sequence to improve expression of the gag and pol proteins, as noted by the Examiner.

Haas *et al.*

The Haas *et al.* reference is cited by the Examiner as teaching "that the *env* gene of HIV-1 has a very pronounced codon bias that apparently, in addition to other regulatory factors, limits expression of the *env* gene"; "that this pronounced codon bias also extends to the *gag* and *pol* genes"; and "that mutating the HIV-1 *env* coding sequence by altering the codon usage for *env* to more closely reflect the codon preference for highly expressed human genes, while still maintaining the wildtype env amino acid sequence, results in much higher levels of expression for the HIV-1 env protein from cytoplasmically transcribed DNA". Office Action dated February 15, 2000 (Paper No. 8), at page 8, line 17 to page 9, line 5.

Haas *et al.* do not teach or suggest retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev proteins and RRE). Haas *et al.* do not teach or suggest packaging cell lines which comprise a packaging construct comprising a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory

proteins or constitutive transport elements. Haas *et al.* do not teach or suggest methods of producing packaging cell lines which comprise co-transfecting mammalian host cells with a packaging construct comprising a codon optimized coding sequence for gagpol proteins, but not coding sequences for viral accessory proteins or constitutive transport elements. As such, the Haas *et al.* reference does not cure the deficiencies of the Naldini *et al.* reference.

Combination of References

In support of the rejection, the Examiner alleges that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the three plasmid system for generating HIV-based packaging cell lines and packaging recombinant HIV-1 particles as taught by Naldini et al to include mutagenesis of the HIV structural genes as taught by Haas et al because Naldini et al teach the efficacy of the three plasmid approach for producing high titre stocks of recombinant HIV-1 particles and because Haas et al teach that it is within the ordinary skill of the art to mutagenize coding sequences for the structural genes of lentiviruses to more closely reflect the codon usage of genes highly expressed in human cells and, consequently, result in dramatically increased levels of production of the HIV structural genes. One would have been motivated to do so in order to receive the expected benefit of generating increased amounts of the gag, pol and envelope components of the recombinant HIV-1 particles, thus generating higher titres of HIV particles from the packaging cell lines, as suggested by Haas et al.

Paper No. 8, at page 9, line 11 to page 10, line 6. Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight. A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S.P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

The claimed invention pertains to packaging cell lines comprising a packaging construct which comprises a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements and to methods of producing packaging cell lines comprising co-transfecting mammalian host cells with a packaging construct which comprises a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements. The claimed invention also pertains to retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev proteins and Rev response element).

Neither of the cited references, alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, the cited references, either alone or in combination, would not have suggested packaging cell lines comprising a packaging construct which comprises a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements or methods of producing packaging cell lines comprising co-transfecting mammalian host cells with a packaging construct which comprises a codon optimized coding sequence for gagpol proteins but not coding sequences for viral accessory proteins or constitutive transport elements. The cited references, either alone or in combination, would not have suggested retroviral vector particles having no viral accessory proteins.

As discussed above, Naldini *et al.* teach HIV-derived retroviral vector particles having all HIV accessory proteins, except the accessory protein Vpu, packaging cell lines comprising a packaging construct which comprises wildtype coding sequences for HIV gagpol proteins and all HIV accessory proteins, except the accessory protein Vpu, and methods of producing packaging cell lines comprising co-transfecting mammalian cells with a packaging construct which

comprises wildtype coding sequences for HIV gagpol proteins and coding sequences for all HIV accessory proteins, except the accessory protein Vpu. Naldini *et al.* teach away from HIV-derived retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev proteins and RRE), and particularly HIV-derived retroviral vector particles lacking viral accessory proteins Tat and Rev. Haas *et al.* teach a method of codon optimization based on the replacement of native codons with codons chosen to more closely reflect the codon preference of highly expressed human genes. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. At best, the cited references merely indicate that specific isolated elements and/or feature recited in the claims are known. This is insufficient to render the claimed invention *prima facie* obvious.

Reconsideration and withdrawal of the rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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